REMARKS

This is filed in response to the Advisory Action dated May 21, 2007, which rejects claims 1-4, and 6-24. Applicants request continued examination of the above-captioned application.

Amendments to the Claims:

Claims 1-4, and 6-24 have been cancelled. Claims 25-47 had been withdrawn from further prosecution by the Applicants in response to a restriction requirement filed May 6, 2006. Applicants have added new claims 48-59 of which claim 48 is an independent claim and claims 49-59 depend on claim 48. The new claims embody the subject matter of the cancelled claims but have been re-written to better describe the Applicant's claimed invention and further clarify the scope of the claims. No new subject matter has been added. Support for new claims 48-59 can be found throughout the specification.

Independent claim 48 recites a composition comprising a biocompatible substrate and genetically altered chondrocytes. The genetically altered chondrocytes are modified to express a therapeutic agent at an ectopic site associated with a disorder. Additionally, the composition is capable of delivering the expressed therapeutic at a level sufficient to ameliorate the disorder. Support for the recitation of claim 48 can be found in the specification, especially in paragraphs 7, 8, 11, 16, 41, and 82 as well as in examples 5-8 of the application as filed.

Dependent claim 49 recites the composition of claim 48 wherein the composition does not become part of the ectopic target region. Additionally, claim 50 pertains to using the composition to deliver a therapeutic agent to an environment surrounding a cell associated with a disorder, so as to modify the environment surrounding the cell. Support for the limitations of claims 49 and 50 can be found in paragraphs 7-9, 13, and 14 of the specification. No new subject matter has been added.

Applicants request the Examiner to enter the new claims and believe that all the new claims are in condition for allowance.

The Applicants Invention:

The instant invention discloses a composition that comprises genetically altered chondrocyte(s) and a biocompatible substrate. The genetically altered chondrocytes are capable of expressing a therapeutic agent in a target region associated with a disorder. The target region is an *ectopic site*; in other words, a site which is *atypical of chondrocytes.* The claimed composition is further capable of delivering the therapeutic agent (expressed by the genetically modified chondrocytes of the composition) at a level sufficient to ameliorate the disorder. Since, the instant invention requires the composition to be delivered to such an atypical chondrocyte environment, it is necessary for the biocompatible substrate of the composition to maintain the viability as well as the functional capability of the genetically altered chondrocytes to express the therapeutic agent. Neither reference cited as the prior art in the office action teach compositions having genetically altered chondrocyte and a biocompatible substrate in the treatment of disorders in atypical chondrocyte environments.

Additionally, claims 57-59 further recite to the desired features of the gel matrix of claim 56. New claim 57 recites to the materials for the gel matrix, while claim 58 recites that the dimensions of the gel matrix determine the concentration of chondrocytes within the matrix. Claim 59, further limits the concentration of chondrocytes in the gel matrix to be about 10,000 to 10 million cells per ml of the matrix volume.

Claim Rejections under 35 USC § 102

Claims 1, 2, 5-14 and 17-24 are rejected by the Examiner under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 6,413,511, (Gloriosos et. al., '511 reference). Additionally, the Examiner has also rejected claims 1-3, and 13-15 under 35 U.S.C. 102(b) as being anticipated by Bartholomew et. al. Applicants have cancelled all the pending claims and have submitted new claims 48-59. The new claims have been re-written to better describe the Applicant's claimed invention and further clarify the scope of the invention. No new subject matter has been added. Applicants believe that the new claims 48-59 represent patentable subject matter in view of both references in the instant office action.

In rejecting the previously pending claims, the Examiner asserted that the '511 reference and the Bartholomew article disclose each and every element of independent claim 1. Applicants respectfully disagree.

The '511 reference teaches a method for introducing a gene of a protein of interest (e.g.: IRAP) into either chondrocytes or synovial cells and the use of such modified cells in *alleviating pathologies of the joint.* The '511 reference is concerned with the treatment of diseased or damaged cartilage tissue using genetically altered chondrocytes or altered synovial cells. Although, the '511 reference discloses a composition consisting of genetically altered chondrocytes and collagen, it only teaches the use of such a composition to repair cartilage tissue by surgically implanting a solid cell-collagen mixture at the site of repair and the use of fibrin glue to retain the cell-collagen mixture at the surgical site (col. 13, lines 20-24). In fact, the main focus of the Glorioso et. al. reference is on the use of genetically altered chondrocytes for the treatment of joint pathologies. The only in-vivo example in this reference discloses the use of chondrocyte-collagen gels to treat articular cartilage defects (see '511, col. 46).

In the current advisory action the Examiner asserts that although Glorioso does not disclose delivering genetically modified chondrocytes to an atypical chondrocyte environment in-vivo, the claimed chondrocytes do not impart any structural difference to the chondrocytes disclosed in Glorioso.

To anticipate a claim, each and every element of the claim must be found in the prior art reference. New claim 48, contains functional limitations that are not present in Glorioso. Namely, claim 48 requires the claimed composition to be capable of delivering the genetically altered chondrocytes to an ectopic site. To achieve this, the claimed composition must be able to deliver viable genetically altered chondrocytes to an ectopic site. Furthermore, the composition should not alter the ability of the modified chondrocytes to express the desired level of therapeutic agent within the environment of the target region. By suggesting that it would be obvious to use the collagen-chondrocyte composition of the Glorioso reference to treat abnormalities in an atypical chondrocyte environment, the Examiner is effectively asserting that *any* combination of a matrix and cells would function in any environment. This is certainly not

the case. Particular matrices may be preferred for use with certain cellular environments. Furthermore, the matrix-cell composition has to be compatible with the region or environment to which it is delivered.

Glorioso only discloses a collagen-chondrocyte composition because such a composition would necessarily have a high chance of success for the treatment of joint pathologies. Collagen is the major component of the cartilage tissue and as mentioned above, and the Glorioso reference focuses on treating joint abnormalities.

Furthermore, there would be no reason for one of ordinary skill, to modify the composition of Glorioso et. al. to deliver genetically modified chondrocytes to an ectopic site, let alone expect the collagen-chondrocyte composition to be functional in repairing or treating pathologies at a site which bears little structural similarity to a joint. For example, it is neither anticipated nor obvious to use chondrocytes to express insulin in the pancreas (see, e.g., para 13 of the specification as filed), or express EPO or EPO mimetibodies to treat anemia, both of which are contemplated in the current specification.

The '511 reference thus fails to disclose or teach all the elements of claim 48, and claim 48 is therefore patentable in view of the '511 reference.

Rejection in View of Bartholomew:

Bartholomew does not anticipate claim 48 as this reference fails to disclose compositions comprising a biocompatible substrate and genetically altered chondrocytes which express a therapeutic agent in an ectopic target region associated with a disorder.

The Bartholomew reference, evaluates the use of genetically altered human or baboon mesenchymal stem cells (bMSC) in gene therapy. Specifically, Bartholomew discloses the use of immunoisolatory devices (IID's) for delivering modified bMSC's expressing human EPO to baboons, and the results from in-vitro and in-vivo studies aimed at determining the level of EPO expressed by cells within the IID's. There is no teaching in Bartholomew of using a biocompatible substrate in place of the IID's to deliver genetically modified cells. Furthermore,

this reference fails to disclose that a composition of cells and a biocompatible substrate would maintain the functional ability of the modified chondrocytes to express a therapeutic agent, especially at a level sufficient to ameliorate the disorder within the ectopic region. Bartholomew, therefore, fails to disclose all the elements of new claim 48, which is patentable over this reference as well. Additionally, Bartholomew does not remedy the deficiencies of the '511 reference. Thus, neither references alone nor in combination teach all the elements of independent claim 48. Claim 48 is therefore patentable over both references.

Patentability of the Dependent Claims over the cited References:

Claims 49-59 depend on independent claim 48 and incorporate all the limitations of this base claim. These dependent claims are therefore patentable over the cited references for at least the same reasons as claim 48. In addition, at least some of the dependent claims are patentable for reasons other than their dependency on claim 48. Claim 49 recites the composition of claim 48, wherein the composition does not become part of the ectopic target region. Claim 50, claims the composition of claim 48 being adapted to deliver a therapeutic agent to an environment surrounding the cells associated with a disorder, and being capable of modifying said cells. Dependent claims 54 and 55 further recite some of the atypical chondrocyte environments to which the claimed composition is delivered. Neither cited reference discloses the recitations of the new claims. In addition, dependent claim 56 recites that the biocompatible substrates of the claimed composition is a gel matrix, while claim 57 requires the gel matrix to be selected from the group consisting of alginate, agarose and polysaccharides. Claims 58 and 59 further recite to the concentration of chondrocytes in the gel matrix. Applicants believe that the recitations of new claims 48-59 are not taught by either cited reference and respectfully request allowance of the pending claims.

Claim Rejections under 35 USC § 103(a)

Claims 4 and 16 are rejected by the Examiner under 35 U.S.C. 103(a) as being obvious over Bartholomew et. al., (Human Gene Therapy, 2001, Vol. 12, p 1527-1541). Applicants have cancelled claims 4 and 16. However, the elements of cancelled claim 4, and 16 are now found in

new claim 53. As discussed above, Applicants believe that the elements of claim 53 distinguish over the Bartholomew reference.

Claim 53 requires that the chondrocytes of the claimed composition have been altered to express an erythropoietin mimetibody. Claim 53 depends on new independent claim 48 and therefore incorporates all of its limitations, and as such claim 53 is neither anticipated nor rendered obvious by Bartholomew at. al.

Bartholomew does not disclose or suggest a composition having a biocompatible substrate and genetically modified chondrocytes, nor does this reference teach using such compositions to express the therapeutic of interest at an ectopic site at a level sufficient to ameliorate the disorder. Bartholomew is concerned with evaluating the use of genetically modified baboon MSC's in gene therapy, particularly, the ability of the modified cells to express hEPO in culture or in-vivo. Thus, Bartholomew does not teach the elements of claim 48 and it certainly does not teach the additional element of claim 53, namely the expression of an erythropoietin mimetibody.

Secondly, Applicants state that the Examiner has failed to establish a case of *prima facie* obviousness. In order to establish a case of *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art references (see MPEP §2143.03 citing *In re Royka*, 490 F.2d 981 (CCPA 1974)). It is clear that the claimed composition is *not obvious* in view of Bartholomew. The Examiner has instead determined that it would be *obvious to try* the teachings of Bartholomew to build the claimed composition; a composition capable of expressing erythropoietin mimetibody when delivered to an ectopic target site.

The Federal Circuit has ruled that in order to show *obviousness* the cited references must suggest how the claimed invention might be achieved. By merely suggesting that it would be obvious to try combining different elements of two distinct inventions to build the applicants claimed invention, does not make the claimed invention obvious. For example, in *Hybritech Inc. v. Monoclonal Antibodies Inc.*, 802 F.2d 1367, 231 USPQ 81 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987), the Federal Circuit ruled that the District court had erred in invalidating the

patent on the grounds that it was *"obvious to try"* using monoclonal antibodies in a sandwich immunoassay for detecting antigens. The Federal Circuit ruled that the cited references did not suggest the claimed invention, rather these references, discussing the production of monoclonal antibodies may constitute "*invitations to try monoclonal antibodies in immunoassays*".

No such showing has been made by either the references or the Examiner. The Examiner's attempt to "build" the Applicants claimed invention is merely a matter of hind-sight. Claim 53 is therefore patentable over Bartholomew and allowance is respectfully requested.

Conclusion

Applicants submit that claims 48-59 are allowable, and allowance thereof is respectfully requested. The Examiner is encouraged to telephone the undersigned attorney for Applicants if such communication is deemed necessary to expedite prosecution of this application.

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Respectfully submitted,

By_____

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